Title

Transcranial direct current stimulation in Parkinson's disease: neurophysiological mechanisms and behavioral effects

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Abstract

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Recent research has highlighted the potential of transcranial direct current stimulation (tDCS) to complement rehabilitation effects in the elderly and in patients with neurological diseases, including Parkinson's disease (PD). TDCS can modulate cortical excitability and enhance neurophysiological mechanisms that compensate for impaired learning in PD. The objective of this systematic review is to provide an overview of the effects of tDCS on neurophysiological and behavioral outcome measures in PD patients, both as a stand-alone and as an adjunctive therapy. We systematically reviewed the literature published throughout the last 10 years. Ten studies were included, most of which were sham controlled. Results confirmed that tDCS applied to the motor cortex had significant results on motor function and to a lesser extent on cognitive tests. However, the physiological mechanism underlying the long-term effects of tDCS on cortical excitability in the PD brain are still unclear and need to be clarified in order to apply this technique optimally to a wider population in the different disease stages and with different medication profiles.

Keywords

- Transcranial direct current stimulation
- Parkinson's disease
- Neuroplasticity

1. Introduction

Although Parkinson's disease (PD) is currently defined as a widespread neurodegenerative disorder, it is largely characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (Berg et al., 2014; Purves et al., 2008). Loss of dopaminergic neurons results in a lack of coordinated activity between the direct and indirect basal ganglia circuits, as described in widely accepted models of the basal ganglia. This in turn induces abnormal activity within cortico-striatal-thalamic pathways of the central nervous system (Albin et al., 1989; Calabresi et al., 2014; DeLong and Wichmann, 2009; DeLong, 1990; Herz et al., 2014). PD is associated with motor symptoms including bradykinesia, tremor, rigidity and postural instability, as well as with a number of non-motor features (Jankovic, 2008). The burden of the disease leads to a significant loss of productivity, early retirement and decreased self-care and other activities of daily living (Jankovic, 2008; Johnson et al., 2011). Dopaminergic medication continues to be the mainstay of medical treatment of PD, despite the fact that its effects diminish and side effects emerge with time (for review see Aquino and Fox, 2015; Beaulieu-Boire and Lang, 2014; Olanow, 2014; Poewe and Antonini, 2015). Another common treatment in PD involves surgical intervention with implantable electrodes stimulating deep brain structures (i.e. deep brain stimulation). However, together with the risk of serious surgical complications, this invasive intervention is only indicated when very specific criteria are met, excluding the majority of PD patients (Sydow, 2008; Weaver et al., 2009). Therapeutic alternatives and rehabilitation interventions as a complementary treatment are therefore required.

Physiotherapy or other methods of targeted training can improve movement and cognitive impairments in PD patients, albeit for a limited time period (Allen et al., 2012; Goodwin et al., 2008; Petrelli et al., 2014; Petzinger et al., 2010; Speelman et al., 2011; Tomlinson et al., 2013). An important requirement to obtain long-term effects of behavioral interventions is the ability

to consolidate new motor skills and store them in the motor memory under the impetus of various mechanisms of neuroplasticity (Penhune and Steele, 2012).

Recent research has highlighted the potential of non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS), to complement and enhance neuroplasticity and learning in patients with neurological disorders and older individuals (for review see Floël A., 2014). TDCS is a technique that elicits constant weak electric currents through the scalp via two electrodes (anode and cathode), which has been shown to modulate excitability in cortical and subcortical tissue (Bindman et al., 1964; Nitsche and Paulus, 2000; Nonnekes et al., 2014; Radman et al., 2009). The central research question of this review builds on these findings by examining the question whether tDCS has an effect on motor and cognitive functioning in conjunction with medication and with or without learning-based interventions in PD. Despite the known advantages of providing spatially specific and concentrated stimulation of transcranial magnetic stimulation (TMS), we will focus on tDCS for reasons of clinical applicability and user-friendliness (Nitsche and Paulus, 2000; Nitsche et al., 2008). The present work will therefore perform a systematic review on the evidence available regarding the effects of tDCS on: (i) cognitive and motor outcomes, (ii) motor learning in PD patients and (iii) possible neurophysiological mechanisms. We will first describe the proposed avenues of neuroplasticity in patients with PD with relevance for the possible response to tDCS.

1.1 Neuroplasticity in Parkinson's disease

The human brain is anatomically and physiologically organized into complex networks, which are indispensable for optimal brain function as well as for the acquisition and performance of activities in daily life. During novel skill learning, several neural processes are responsible for the reorganization of specific changes in the patterns of intracortical and subcortical-cortical connectivity (Doyon et al., 2009; Landi et al., 2011; Penhune and Steele, 2012). A recent motor sequence learning model proposed a distinct role of the cerebellum, basal ganglia and primary

motor cortex (M1) in motor learning, depending on task demands and the learning stage (Penhune and Steele, 2012).

Motor learning is a relatively permanent change in the capability of a person to execute motor skills as a result of practice or experience (Schmidt and Lee, 1999). It has been studied from different perspectives and a distinction between motor sequence learning (i.e. acquisition of a new sequence of movements) and motor adaptation (i.e. adaptation to environmental changes) can be made (Doyon and Benali, 2005; Doyon and Ungerleider, 2002; Doyon et al., 2003). Motor skill learning proceeds through a fast acquisition phase and a slow consolidation and automatization phase. The basal ganglia are involved in all phases of motor skill learning, though particularly during motor sequence learning in the later stages, i.e. during consolidation and automatization (Agostino et al., 2004; Diedrichsen et al., 2005; Doyon and Ungerleider, 2002; Doyon et al., 2009; Grafton et al., 1995; Laforce and Doyon, 2002; Rauch et al., 1997; Wu and Hallett, 2005). Both behavioral and brain imaging studies have investigated whether (re)learning of motor skills is possible in patients with PD and whether this is correlated with changes in brain activity. Results showed that the efficiency achieved as a result of learning is reduced in PD patients compared with healthy controls (Felix et al., 2012; Smiley-Oyen et al., 2006; Stephan et al., 2011; Swinnen et al., 2000). To compensate for basal ganglia dysfunction, patients recruit additional brain regions and show alterations in effective connectivity to reach similar levels of performance (Mentis et al., 2003; Sehm et al., 2014; Wu and Hallett, 2005; Wu et al., 2014, 2012, 2010). Patients are thus able to improve their performance as a result of practice, though their ability to acquire new motor sequences and consolidate acquired skills is affected (Abbruzzese et al., 2009; Doyon, 2008; Felix et al., 2012; Marinelli et al., 2009; Moisello et al., 2015; Nackaerts et al., 2013; Nieuwboer et al., 2009; Ruitenberg et al., 2015; Terpening et al., 2013; Venkatakrishnan et al., 2011). Moreover, when patients with mild PD achieve automaticity of a motor task via compensatory strategies, re-attention to the task results

in a disruption of this modified automatic mode within the striatum (Wu et al., 2014). Thus, the difficulties in learning and performing skills in an automatic fashion, as observed in PD, may be due to the primary neural deficit in the basal ganglia on the one hand and secondary spontaneous alterations in neural excitability in additional brain areas on the other (Kishore et al., 2012).

Neuroplasticity is the physiological mechanism that enables the brain to encode experiences and reorganize itself. It can be defined as the modification of existing neural networks in response to changes in behavior or environment (Pascual-Leone et al., 2005; Rossini et al., 2007). It has been shown that the same neural mechanisms underlying normal reorganization are responsible for relearning skills in the damaged brain as a result of neurological disorders (Kleim and Jones, 2008; Monfils et al., 2005). At the synaptic level (i.e. synaptic plasticity), long-term potentiation (LTP) and long-term depression (LTD) cause activity-dependent modifications in synaptic efficacy (Südhof and Malenka, 2008). These neurophysiological processes play an important role in the storage of information and are therefore key mechanisms in memory and learning (Malenka, 1994; Ziemann and Siebner, 2008). LTD and LTP appear to be controlled and modulated by dopamine from nigrostriatal pathways (Schroll et al., 2014; Shen et al., 2008). Moreover, LTP and corticostriatal synaptic plasticity can be restored by the long-term application of dopaminergic medication or the transplantation of dopamine neurons in Parkinsonian rats (Picconi et al., 2003; Rylander et al., 2013).

Alterations in dopaminergic transmission may influence cerebral reorganization, i.e. plasticity at the neurological systems level, via the direct and indirect pathways and their interaction with the basal ganglia-thalamo-cortical circuits (Helmich et al., 2010; Nitsche et al., 2006). This is in line with previous studies in PD patients that also showed altered plasticity of neurons in the basal ganglia and related subcortical structures as well as in M1 (Schroll et al., 2014; Udupa and Chen, 2013). The aberrant plasticity in PD may be directly responsible for the decreased

memory and learning capacity observed in patients and plays an essential role in the development of Parkinsonian symptoms (Calabresi et al., 2007; Schroll et al., 2014).

M1 is considered to be an important output node of the basal ganglia network and plasticity of this area has been investigated extensively in PD patients (Bologna et al., 2015; Suppa et al., 2010; Udupa and Chen, 2013). Studies using paired associative stimulation to measure LTP-like plasticity at cortical synapses found altered plasticity, as reflected by changes in cortical excitability, in both de novo and more advanced PD patients in the OFF-phase of the medication cycle (Kojovic et al., 2012; Morgante et al., 2006; Ueki et al., 2006). The alterations in M1 excitability seemed to normalize with dopaminergic medication (Morgante et al., 2006; Ueki et al., 2006). Interestingly, Kojovic *et al* (2012) demonstrated increased excitability of M1 and functional reorganization of the sensorimotor cortex in early PD patients at the least affected side, which was not present at the most affected side showing reduced plasticity and inhibition. A recent longitudinal study further substantiated this finding by showing that hemispheric asymmetry of sensorimotor cortical plasticity was still present after 1 year follow-up (Kojovic et al., 2015). The changes in cortical plasticity were negatively correlated with the severity of clinical symptoms and might therefore reflect compensatory changes. Intriguingly, comparisons between those who started dopaminergic medication over the course of the year and those who did not revealed no differences in plastic changes, a finding which could be confounded by the small sample size of this study (Kojovic et al., 2015, 2012). In addition, a recent functional magnetic resonance imaging (fMRI) study demonstrated increased functional connectivity between the subthalamic nucleus and the sensorimotor cortex at the most affected side in de novo and moderate PD patients, which was positively correlated with motor symptoms (Kurani et al., 2014).

Taken together, these findings imply that difficulties in sequential movement learning and consolidation in PD patients may be associated with essential neuroplasticity changes in the

basal ganglia and related (sub)cortical structures. This points to the need to understand and modulate this altered excitability in each hemisphere to facilitate optimal learning in PD.

1.2 Neuroplasticity and tDCS

Non-invasive stimulation with tDCS and TMS is able to enhance neuroplasticity processes at least in healthy elderly (for review see Zimerman and Hummel, 2010). Previous systematic reviews have demonstrated that repetitive TMS (rTMS) can improve motor function in PD (Chou et al., 2015; Elahi et al., 2009; Fregni et al., 2005; Zanjani et al., 2015; Zhu et al., 2015) Moreover, it was recently demonstrated that the application of TMS over the right posterior parietal cortex after targeted visuomotor training enhanced the retention of a newly acquired motor skill in PD for at least 24 hours (Moisello et al., 2015). Although both TMS and tDCS have the potential to modulate cortical excitability, resulting in immediate and long-term effects, tDCS is considered to have more therapeutic potential as it is safer, less costly and more user-friendly (Liu et al., 2013; Nitsche and Paulus, 2000). TDCS elicits constant weak electric currents which modulates excitability by inducing alterations of neuronal resting membrane potentials in cortical and subcortical tissue (Bindman et al., 1964; Nitsche and Paulus, 2000; Nonnekes et al., 2014; Radman et al., 2009). Additionally, other mechanisms such as dynamic modulation of synaptic efficacy and the induction of the release of neurotransmitters may be involved as well (Parasuraman and McKinley, 2014; Stagg et al., 2009; Tanaka et al., 2013). A possible beneficial effect of tDCS stimulation specific for PD patients could be the induction of dopamine release in the caudate nucleus via the glutamatergic corticostriatal pathways as was shown in animal studies (Li et al., 2011; Lu et al., 2015; Strafella et al., 2001; Tanaka et al., 2011; Whitton, 1997). Recently, it was suggested that tDCS may also have a neuroprotective role in PD by reducing the oxidative damage of dopaminergic neurons (Lu et al., 2015). Moreover, it was found that tDCS modulates functional connectivity of the cortico-striatal and thalamo-cortical circuits in the human brain (Polanía et al., 2011). The long-term

neuroplasticity effects of tDCS on M1 were proposed to be based on several processes that accompany motor learning such as LTP via modulating intracellular signals by increasing the net calcium influx into the targeted cortical neurons after stimulation (Karabanov et al., 2013). In addition, tDCS may adjust resting membrane potentials mediated by changes in N-methyl-D-aspartate-receptor activation and GABAergic inhibition (Liebetanz et al., 2002; Paulus et al., 2008; Stagg et al., 2009; Tanaka et al., 2013). Orban de Xivry and Shadmehr (2014) proposed three polarity-dependent key principles underlying the effects of tDCS on motor control and learning: (i) the alteration of neuronal firing rates (i.e. the increase by anodal and decrease by cathodal stimulation), (ii) the strengthening and stabilization of newly formed associations in the cerebral cortex by anodal polarization and (iii) the formation of new and/or preferred firing pattern of neurons in memory after anodal stimulation. The authors stated that the first principle may be responsible for the direct effects of tDCS on motor performance. The second and third principle on the other hand could be linked to the acquisition and consolidation phases of motor learning and particularly relevant for use in combination with behavioral interventions in PD (Orban de Xivry and Shadmehr, 2014). Thus, tDCS has the potential to influence synaptic plasticity, which may enhance training-induced learning in PD.

TDCS was also shown to modulate cognitive function in healthy young and older subjects (Boggio et al., 2010; Fertonani et al., 2014; Harty et al., 2014; Zaehle et al., 2011). As in motor learning, tDCS was suggested to influence cognitive networks by altering cortical excitability in key cognitive regions which are potentially penetrable such as the dorsolateral prefrontal cortex (DLPFC) (Miniussi et al., 2013). In PD, this area has been implicated in executive function impairment through the dopaminergic dysfunction of the striatofrontal network and top-down attentional dysfunction through alterations in the cholinergic frontoparietal circuits (Gratwicke et al., 2015). Indirectly, by improving cognitive function, it was suggested that motor control is likely to be affected as well (Orban de Xivry and Shadmehr, 2014). The

schematic diagram in Figure 1 gives an overview of the relationships between the potential short and long-term benefits of tDCS in PD.

Though increased excitability of cortical areas by tDCS may induce spontaneous compensatory neural activity and result in direct symptomatic benefits for patients with PD, the exact relationship between alterations in neuroplasticity and clinical motor and cognitive symptoms is still unclear (Bologna et al., 2015). To further investigate this question, we performed a systematic review focusing on studies that assessed the effects of tDCS in PD patients.

2. Methods

2.1 Search strategy

We systematically reviewed the literature published throughout the last 10 years on the use of tDCS stimulation in PD. Electronic databases including Medline (PubMed), EMBASE and Central (Cochrane) were searched. The following search terms were used and combined to select the most relevant articles: Parkinson disease, Parkinson*, transcranial direct current stimulation and tDCS. Subsequently, two researchers (SB and EN) independently scanned titles and abstracts of articles to identify relevant articles for full-text retrieval. Any disagreements between researchers were resolved by a third researcher (EH).

2.2 Selection criteria

For the purpose of this review, we only included studies using tDCS as the intervention of interest in patients with PD. Four explicit inclusion criteria were adopted: (i) studies assessing the effects of tDCS on either motor or cognitive function; (ii) studies examining the effect of tDCS on learning; (iii) studies incorporating neurophysiological measurements and (iv) articles including all types of PD patients without limitations for disease severity. Studies were excluded when they examined the effects of other non-invasive brain stimulation techniques (e.g. rTMS or transcranial alternating current stimulation) or combined paradigms with both tDCS and rTMS as intervention. Animal studies, review articles and studies published in abstract form were also excluded.

2.3 Data extraction

Based on full text articles, data were extracted by two researchers independently (SB and EH) using a standardized data extraction form. Any uncertainties were referred to another researcher (EN) and resolved by consensus. A descriptive analysis was conducted to evaluate and

summarize key parameters regarding study design, participants, intervention and outcome measures of the included studies. In addition, where possible, the Cohen's d effect size was calculated to estimate differences in performance of pre- and post tDCS interventions.

3. Results

After running the search strategy and the implementation of inclusion and exclusion criteria, we identified a total of ten studies that were eligible for review (see figure 2 and table 1 for characteristics and results). The methodological quality of studies was on average well controlled with some exceptions. Five studies were randomized controlled trials that used either a double- or single-blind design (Benninger et al., 2010; Boggio et al., 2006; Kaski et al., 2014b; Valentino et al., 2014; Verheyden et al., 2013). However, four of these studies used a crossover design (Boggio et al., 2006; Kaski et al., 2014b; Valentino et al., 2014; Verheyden et al., 2013). Nine of the included studies were sham controlled (Benninger et al., 2010; Boggio et al., 2006; Doruk et al., 2014; Fregni et al., 2006; Kaski et al., 2014a, 2014b; Manenti et al., 2014; Valentino et al., 2014; Verheyden et al., 2013) and one study compared tDCS of the dorsolateral prefrontal cortex (DLPFC) with temporo-parietal cortex (TPC) stimulation (Pereira et al., 2013). Table 1 also shows that patient characteristics varied greatly in the 10 included studies, with mean disease durations ranging from 7 to 13.2 years and Hoehn and Yahr (H&Y) scores ranging from I to IV. The mean age of the participating patients ranged from 61 to 72 year. Otherwise, studies showed large variability regarding specific characteristics of the stimulation protocol (e.g. number of stimulation sessions, site of stimulation, medication status and duration) as well as type of motor and cognitive assessments performed. Clinical and methodological heterogeneity precluded pooling of results. Only three studies used tDCS in multiple sessions (Benninger et al., 2010; Doruk et al., 2014; Valentino et al., 2014) and in one study tDCS was employed concurrently with physical training (Kaski et al., 2014b). The studies will be discussed in detail in the next section by grouping the effects of tDCS on (i) neurophysiological parameters, (ii) motor skills and (iii) cognitive functioning.

3.1 Neurophysiological effects of tDCS in Parkinson's disease

Only one study measured the impact of tDCS, applied during one session, on cortical excitability in patients with PD (see table 1) (Fregni et al., 2006). After anodal, cathodal and sham stimulation over M1, characteristics of motor evoked potentials (MEP) were collected using single pulse TMS and correlated with improvements in motor function. Results revealed significantly increased MEP amplitudes and areas under the curve after anodal M1 stimulation was compared to sham. In contrast, cathodal tDCS decreased the MEP amplitude and the area under the curve. Changes in MEP characteristics tended to correlate with motor improvements as measured by the UPDRS-III and suggested an enhancement of cortical excitability after stimulation (Fregni et al., 2006). Noteworthy is that these results were obtained while patients were in the OFF-phase of the medication cycle. Pereira *et al.* (2013) used fMRI to assess functional brain connectivity and task-related activation and deactivation patterns after one session of anodal tDCS at the DLPFC and at the TPC as a control region (see table 1) (Pereira et al., 2013). Patients performed a verbal fluency paradigm (a test of executive function) in the scanner immediately after stimulation while ON medication. Significant changes of the BOLD-response in favor of anodal tDCS over the DLPFC compared to stimulation over the TPC were found in functional networks, involving frontal, parietal and fusiform brain areas (Pereira et al., 2013). These preliminary results suggest that tDCS seemed to influence the BOLD response in the regions of interest globally.

3.2 Effects of tDCS on motor function in Parkinson's disease

3.2.1 Effects of tDCS on the UPDRS part III

Four studies used the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) to assess overall motor function in patients with PD before and after tDCS (see table 1)

(Benninger et al., 2010; Doruk et al., 2014; Fregni et al., 2006; Valentino et al., 2014). All four studies applied tDCS for 20 minutes during rest, though the number of sessions and stimulation intensity varied. Two of these studies showed a statistically significant effect on the UPDRS-III in favor of anodal tDCS over M1 compared to sham stimulation (Fregni et al., 2006; Valentino et al., 2014). Fregni *et al*. (2006) found an immediate effect on motor performance after one session of anodal stimulation over M1 during the OFF-phase of the medication cycle. This result was polarity-dependent since cathodal and sham stimulation of M1 were not significantly different. Moreover, comparing anodal stimulation of the DLPFC with sham also revealed no significant differences (Fregni et al., 2006). Of note, these improvements were gained using 1.0 mA stimulation intensity and a current density of 0.021 mA/cm^2. After five stimulation sessions in the ON-phase, Valentino *et al.* (2014) found no significant improvements one day post-intervention. However, delayed effects of stimulation were shown by significantly decreased UPDRS-III scores five days, seven days, two weeks and four weeks after stimulation compared to sham (Valentino et al., 2014). The remaining two studies only showed non-significant effects of anodal tDCS stimulation on UPDRS motor performance (Benninger et al., 2010; Doruk et al., 2014). Both studies applied multiple anodal tDCS sessions, though different stimulation sites were used (i.e. DLPFC (Doruk et al., 2014) and a combination of M1, premotor cortex and prefrontal cortex (Benninger et al., 2010)).

3.2.2 Effects of tDCS on upper limb performance

Four studies examined the effects of tDCS on upper limb performance tests (see table 1) (Benninger et al., 2010; Doruk et al., 2014; Fregni et al., 2006; Pereira et al., 2013). While the study of Benninger *et al*. (2010) demonstrated no important changes in UPDRS scores, it did show a statistically significant effect on the time to perform upper limb movement sequences after eight sessions of anodal stimulation (M1, premotor cortex and prefrontal cortex) in the

ON-phase compared to sham and baseline. These results were sustained in the long-term follow-up at one and three months and involved large effect sizes (see table 1) (Benninger et al., 2010). Another study used anodal tDCS over M1 during the OFF-phase of the medication cycle and showed that Purdue Pegboard Test performance tended to improve after one active stimulation session compared to sham. In the same study no improvements were found after cathodal stimulation of M1 and anodal stimulation of the DLPFC (Fregni et al., 2006). Two studies that used anodal DLPFC stimulation alone showed no significant effects on upper limb performance as tested by the Purdue Pegboard Test and by the evaluation of buttoning and supination-pronation movements after respectively one and ten stimulation sessions in the ON-phase of the medication cycle (Doruk et al., 2014; Pereira et al., 2013).

3.2.3 Effects of tDCS on gait

The effects of tDCS on gait in PD patients were tested in seven out of the ten reviewed studies (see table 1) (Benninger et al., 2010; Doruk et al., 2014; Kaski et al., 2014a, 2014b; Manenti et al., 2014; Valentino et al., 2014; Verheyden et al., 2013). When comparing anodal tDCS and sham stimulation, four studies found significant effects on several parameters of gait performance which in one study persisted for four weeks after intervention (Benninger et al., 2010; Kaski et al., 2014a; Manenti et al., 2014; Valentino et al., 2014). In addition, Valentino *et al.* (2014) showed significant interactions between stimulation condition and time for the number and duration of freezing episodes during gait, as well as a significant amelioration on the Freezing of Gait Questionnaire as compared with baseline (Valentino et al., 2014). The stimulation protocols of these four studies varied greatly with differences in number of sessions, intensity and duration (see table 1). Interestingly, three of four studies stimulated M1 (Benninger et al., 2010; Kaski et al., 2014a; Valentino et al., 2014), whereas the one study that applied tDCS over the right DLPFC showed greater improvements and a large effect size when

brain areas contralateral to the more affected side were stimulated (see table 1) (Manenti et al., 2014). When the effects of bihemispheric tDCS (left and right premotor cortex and M1) with and without contemporary gait training were compared by Kaski *et al.* (2014b), a significant benefit of combining anodal tDCS with physical training was found and involved moderate to large effect sizes (see table 1). These relative improvements on gait performance were greater for the combination of stimulation and gait training than the effects of physical training alone. Bihemispheric tDCS administered without training was not shown to be beneficial. In another study, ten sessions of DLPFC stimulation failed to show significant effects on walking time (Doruk et al., 2014). Furthermore, negative results of tDCS were found in a study that showed a decrease in walking velocity after 1.0 mA anodal M1 stimulation (current density 0.029 mA/cm^2) compared to sham (Verheyden et al., 2013).

3.3 Effects of tDCS on cognitive function in Parkinson's disease

Three studies that investigated the effects of tDCS on cognitive function found significant improvements of different aspects of cognitive function after anodal stimulation of the DLPFC (see table 1) (Boggio et al., 2006; Doruk et al., 2014; Pereira et al., 2013). Boggio *et al*. (2006) demonstrated a significantly higher accuracy during a working memory paradigm after one session with 2.0 mA DLPFC stimulation (current density 0.057 mA/cm^2), although no significant effects were found after 1.0 mA M1 stimulation (current density 0.029 mA/cm^2). Effect sizes of 1.0 mA and 2.0 mA DLPFC stimulation were moderate and large, respectively (see table 1) (Boggio et al., 2006). This is in accordance with another study that showed significant improvements of phononemic verbal fluency after tDCS over the DLPFC (Pereira et al., 2013). Doruk *et al* (2014) found that executive function, as measured by the Trail Making Test, progressed after both anodal and sham tDCS, which may have been due to a learning effect. However, only patients in the active stimulation groups showed significantly lasting improvements after one month follow-up (Doruk et al., 2014).

4. Discussion

This review aimed to provide a comprehensive overview of the knowledge gained in the last 10 years on the effects of tDCS stimulation on neurophysiological and behavioral outcome measures in PD. Taken together, the few studies that investigated tDCS in PD revealed large heterogeneity in stimulation parameters, study designs and outcome measures. This heterogeneity may partly explain the large variation of the effects of tDCS that have been reported on behavioral outcomes in PD. Despite the difficulty of drawing definitive conclusions from these results, overall, studies show a consistent tendency towards positive effects of tDCS for patients with PD. The behavioral effects of tDCS support the efficacy of anodal stimulation of M1 in improving motor function, although not unequivocally. In addition, there was some evidence that stimulation of the DLPFC improved executive function. It is, however, less clear which mode of stimulation leads to the best results and whether stimulation should be done best ON or OFF medication. There is also still limited evidence on using tDCS as an adjunct to motor learning. Several factors may play an essential role in explaining these varied results of using tDCS in PD, which will be discussed in the following sections.

4.1 The effect of polarity and site of stimulation

Excitatory and inhibitory mechanisms after different polarities of stimulation can be measured with paired pulse TMS on M1. However, so far, the evidence on cortical excitability changes in PD due to tDCS is very limited and does not provide differential information on which inhibitory or excitatory circuits in M1 lead to increased MEPs after anodal tDCS or decreased MEPs after cathodal tDCS. In line with findings in healthy subjects and stroke patients (for review see Bastani and Jaberzadeh, 2012; Lüdemann-Podubecká et al., 2014), the neurophysiological measurements in PD indicated a polarity-dependent effect on cortical excitability in favor of anodal stimulation compared to cathodal stimulation (Fregni et al.,

2006). These effects were correlated to improvements in motor performance. A meta-analysis on the effects of TMS in PD reiterated these results by showing that increased M1 excitability induced by high-frequency rTMS reduced patients' motor signs (Elahi et al., 2009). In addition, rTMS over the supplementary motor area in PD patients resulted in a decreased threshold for excitability in M1 together with improved fine motor task performance (Randhawa et al., 2013). Several studies in PD also showed differential effect of tDCS depending on the site of stimulation (Boggio et al., 2006; Doruk et al., 2014; Fregni et al., 2006; Manenti et al., 2014; Pereira et al., 2013). The increased cognitive skill performance after DLPFC anodal stimulation and improved motor performance after M1 stimulation, expresses this regional specificity. In this regard, the study by Manenti *et al.* (2014) indicated an exception, as anodal DLPFC stimulation appeared to improve motor performance. This study also showed greater improvements and a larger effect size when brain areas contralateral to the more affected side were stimulated (Manenti et al., 2014). These results are in line with studies in healthy subjects and stroke patients and the contention that tDCS effects are largely site-specific, though not site limited (Fregni and Pascual-Leone, 2007; O'Shea et al., 2014; Saucedo Marquez et al., 2013). Moreover, physical training combined with bihemispheric stimulation to increase excitability in both cortical leg areas seemed to be beneficial for an axial task such as gait (Kaski et al., 2014a, 2014b, 2012). In conclusion, facilitating effects of tDCS in PD patients seem to be dependent on the degree to which the stimulated brain areas are involved in the nature of the performed task.

4.2 Intensity-dependent effects, current density and the influence of dopaminergic medication

Other essential methodological aspects determining the effects of tDCS stimulation are the stimulation intensity (mA) and current density (mA/cm^2). Although tDCS intensities of 1.0 mA on M1 were already shown to increase cortical excitability, higher stimulation intensities up to

2.0 mA may even be more beneficial to enhance performance in PD (Fregni et al., 2006). Findings by Boggio *et al*. (2006) support this hypothesis showing a significantly larger effect on accuracy in a working memory paradigm after stimulation at 2.0 mA (current density 0.057 mA/cm^2) rather than 1.0 mA (current density 0.029 mA/cm^2), which was also reflected in the effect sizes of both interventions (i.e. large and moderate, respectively). In accordance, studies in healthy adults showed that larger stimulation intensities during motor learning enhanced skill acquisition compared to sham and lower intensities (Cuypers et al., 2013). This may result from the fact that higher current intensities lead to increased activity-dependent modifications in synaptic efficacy and thus enhance performance and learning. In PD, baseline M1 excitability changes are likely to be different from those in healthy older adults and vary with disease duration (Buhmann et al., 2004; Kojovic et al., 2015). Therefore, using higher stimulation intensities in itself may also be counterproductive in case of aberrant plasticity, when lack of inhibitory influences and disinhibition have already reached a ceiling effect or play a negative role. Future studies need to address this issue in different cohorts of patients. Reducing electrode size resulted in more focal stimulation and current densities (mA/cm^2) were higher (Nitsche et al., 2007). However, stimulation intensity and current density needs to be adapted with caution, as intensities higher than 3 mA are reported to be painful (Furubayashi et al., 2008).

Interestingly, there may also be a link between the required intensity and the intake of dopaminergic medication. Two of the included studies administered tDCS while PD patients were OFF medication and both studies demonstrated improvements in performance after 1.0 mA anodal stimulation (current densities 0.029 mA/cm^2) (Boggio et al., 2006; Fregni et al., 2006). This may point to lower excitability thresholds in the OFF-phase. In contrast, when 1.0 mA stimulation (current density 0.029 mA/cm^2) was applied during the ON-phase, a negative effect of anodal tDCS on gait performance was found (Verheyden et al., 2013). All other studies performed in the ON-phase of the medication cycle used higher stimulation intensities of 2.0

mA (Benninger et al., 2010; Doruk et al., 2014; Kaski et al., 2014a, 2014b; Manenti et al., 2014; Pereira et al., 2013; Valentino et al., 2014). Neurophysiological studies in PD using TMS showed that alterations in corticospinal measures, such as short-interval intracortical inhibition and silent period, can be normalized by dopaminergic medication (Priori et al., 1994; Ridding et al., 1995). This, however, was contradicted by a recent study of Kojovic *et al.* (2015) finding no differences for TMS parameters between treated and untreated patients (Kojovic et al., 2015). The application of medication might thus interact with tDCS or influence the threshold for effective intensities of transcranial stimulation. Future studies are needed to gather more insights in the most optimal current densities and its interacting effects with dopaminergic medication to establish the best stimulation parameters in PD.

4.3 The impact of disease severity, disease duration and age

Together with substantial differences in methodology, the available tDCS studies in PD also demonstrated large heterogeneity in patient characteristics. This could have been another important factor for the observed differences in effectiveness between studies. PD is a progressive neurodegenerative disease that results in significant cortical alterations and reorganization (Herz et al., 2014; Kalmar et al., 2011; Kojovic et al., 2015). Optimal stimulation parameters to enhance specific alterations in plasticity might therefore vary greatly with disease duration and severity. A recent longitudinal TMS study showed that changes in cortical plasticity are negatively correlated with the severity of clinical symptoms in PD patients (Kojovic et al., 2015). Previous brain imaging studies also showed a decreased BOLD response in the supplementary motor area and DLPFC in PD compared to controls in various disease stages (Herz et al., 2014; Kurani et al., 2014; Michely et al., 2015; Wu and Hallett, 2005; Wu et al., 2012). Thus, anodal stimulation to enhance cortical excitability in specific areas seem to be justified for patients across the disease spectrum (Haslinger et al., 2001; Rascol et al., 1994; Sabatini et al., 2000). Regarding stimulation of M1, results are more controversial. In early and

untreated PD patients, reduced BOLD responses of M1 were found, whereas in more advanced patients M1 was shown to be hyper-activated (Buhmann et al., 2003; Haslinger et al., 2001; Sabatini et al., 2000). Changes in M1 activity in the later stages of the disease might reflect a compensatory mechanism dependent on cortical reorganization and plasticity processes (Helmich et al., 2010). The influence of tDCS on these spontaneous adaptive mechanisms during the course of PD needs further in-depth study.

An additional important factor to consider in tDCS application is age, as studies using rTMS and paired associative stimulation found a different response to non-invasive brain stimulation in older compared to younger subjects (Fathi et al., 2010; Pellicciari et al., 2009; Tecchio et al., 2008; Todd et al., 2010). This may be explained by age-related adaptations as well as differences in LTP-like processes (Goodwill et al., 2013; Zimerman and Hummel, 2010). In the studies included in this review, the mean age ranged from 61 to 72 years. Up to now, several proof of principle investigations of tDCS in elderly showed a beneficial effect of anodal stimulation as an adjunct to motor learning which is in line with the promising effects of tDCS in PD reviewed here (Flöel et al., 2012; Hummel et al., 2010; Parikh and Cole, 2014; Zimerman et al., 2013).

4.4 TDCS as adjunctive tool to motor learning

In older people it has been suggested that the application of tDCS during motor learning can have additive effects on the LTP-like mechanism of its action and prolong improvements of performance (Zimerman and Hummel, 2010; Zimerman et al., 2013). Given that a tDCS device is small, relatively inexpensive, portable and suitable for at-home-use, it has the potential to become a usable adjunct to current neurorehabilitation strategies. To date, only one study investigated the effects of tDCS combined with physical training in PD (Kaski et al., 2014b). Kaski *et al*. (2014) demonstrated a significant benefit and large effect sizes for anodal stimulation during gait rehabilitation in patients with PD compared to tDCS or physical training

alone. Similar results were found using rTMS applied with treadmill training, showing an enhancing effect of stimulation on corticomotor excitability and walking performance (Yang et al., 2013). This is in concordance with previous literature in healthy subjects and elderly showing that long-term retention and consolidation of motor skills were enhanced by tDCS and TMS (Flöel et al., 2012; Goodwill et al., 2013; Hummel et al., 2010; Karok and Witney, 2013; Parikh and Cole, 2014; Reis et al., 2009; Waters-Metenier et al., 2014; Zimerman et al., 2013). Importantly, consolidation mechanisms were susceptible to anodal tDCS, which suggested an additive effect of stimulation especially for offline learning processes (Flöel et al., 2012; Reis et al., 2009). In stroke patients, bihemispheric tDCS induced a transfer of improved performance to an untrained task and tDCS enhanced the long-term retention (Lefebvre et al., 2014). Given the limited consolidation of learning predicted by basal ganglia dysfunction, tDCS as adjunct to physical therapy could therefore be an instrumental intervention to enhance the neurophysiological mechanisms that compensate for impaired consolidation in PD.

4.5 Future perspectives and challenges

Although the results of tDCS interventions in PD are still preliminary, they encourage further in-depth studies to define its role in the treatment of the disease. For tDCS to become a relevant clinical tool in PD, it must show to have positive, durable and lasting effects on cortex excitability and activities of daily living. Additional studies should be performed and designed to investigate how the specific pathophysiological profile of PD patients and disease stage affects the response to tDCS. Possible interactions with pharmacological interventions and the utility of tDCS concurrently with learning paradigms should be studied before designing large randomized controlled trials. Standardization of the methodology for effective neural facilitation or inhibition and protocols to achieve reproducibility are necessary (e.g. stimulation intensity, stimulation duration and electrode attachment, montage and size). The effects of different stimulation procedures need to address the potential therapeutic advantages of tDCS

as an adjunctive tool in PD rehabilitation. Moreover, future tDCS experiments should integrate functional imaging techniques to confirm the causal relation between alterations in neuroplasticity and observed behavioral effects.

5. Conclusion

The present review showed that tDCS can have significant positive effects on motor and cognitive functioning in patients with PD. However, more insight in optimal stimulation parameters for the development of PD specific protocols, such as site of stimulation and intensity, is necessary. The lack of convincing evidence for neurophysiological effects of tDCS implies that more proof of principle studies using cortical excitability outcome measures are needed before robust conclusions in relation to clinical outcomes can be drawn. These insights may pave the way for the development of treatment strategies combining tDCS and motor learning, resulting in the development of more cost-effective and evidence-based rehabilitation programs in PD.

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Figure captions

Figure 1. Relationships between the potential effects of tDCS in PD. Compensatory neural activity and direct symptomatic benefits may be immediate effects of tDCS. Alterations in neuroplasticy and enhanced consolidation of learning are possible long-term adaptations after tDCS.

Figure 2. Flow diagram of the screening process and categorization of the included articles. *Studies with multiple outcomes are included in more than one category where appropriate.

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